Hunterian Lecture

ON

UTERINE HÆMORRHAGE

H. BECKWITH WHITEHOUSE

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ON THE

PHYSIOLOGY AND PATHOLOGY OF UTERINE HÆMORRHAGE

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BY

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Hunterian Lecture

ON

THE PHYSIOLOGY AND PATHOLOGY OF UTERINE HÆMORRHAGE.

Mr. President, Ladies, and Gentlemen,—My first pleasant duty is to thank you for the honour you have conferred upon me in appointing me one of your Hunterian professors for the current year.

Introduction.

In selecting Uterine Hæmorrhage as the subject of this lecture I have been guided mainly by two factors. In the first place, it affords me the opportunity of placing before you the results of some researches in which I have been engaged. Secondly, the present appears to be an appropriate time for discussing some of the older views upon uterine bleeding based principally upon clinical observation, in the light of that more exact knowledge which scientific study and laboratory experiment have placed at our disposal.

John Hunter himself was much interested in the phenomena associated with the blood and its coagulation, as is shown by the publication in 1792 of his " Treatise on the Blood." This fact in itself provides another very good reason why we should choose that organ of the body where hæmorrhage is not only a pathological but a physiological function to form the basis of a lecture founded in his memory.

Uterine hæmorrhage, however, in all its varied aspects is far too large a question to take up in the time at my disposal. I propose, therefore, to limit remarks upon pathological bleeding to its incidence apart from pregnancy and uterine neoplasms. Such hæmorrhage is sometimes termed idiopathic, to denote the absence of gross physical signs. A clear understanding of the facts underlying pathological bleeding must rest upon a true interpretation of the phenomena associated with physiological hæmorrhage, and therefore the first portion of the lecture is devoted to facts concerned with the etiology and physiology of the function known as menstruation.

PHYSIOLOGICAL UTERINE HÆMORRHAGE.

The Relation of Menstruation to Pro-œstrum.

Matthews Duncan once observed that "menstruation is like the red flag outside an auction sale. It shows that something is going on inside." This is obviously true, but we may pause to ask whether such bleeding is physiologically necessary to the sexual economy. A comparative study of the mammalia shows that uterine hæmorrhage is by no means an essential but merely a concomitant of the sexual cycle and is associated with those anatomical changes to which Heape has applied the name of pro-œstrum. There is abundant evidence that a phenomenon in all essentials identical with menstruation in the human female occurs in the case of the lower mammals. Attention was first drawn to the similarity between menstruation and pro-œstrum by Wiltshire in 1883. More recently the excellent work of Heape and Marshall and Jolly have confirmed the views originally set forth.

It is not my wish to go into detail upon this subject, which has been so admirably treated by other workers. It is sufficient to point out that in most animals the stage of pro-œstrum is marked by the presence of a discharge from the generative canal. In some, such as the rabbit and the rat, this discharge consists simply of the secretion of the uterine glands with a small quantity of degenerated epithelium. In others, of which the cow, mare, sheep, goat, pig, and cat are examples, this discharge is occasionally mixed with blood. Domesticity and high breeding tend to increase both the frequency of the sexual cycles and the amount of the attendant bleeding. Thus, in the bitch a well-marked hæmorrhagic discharge is almost invariably present during pro-œstrum, and the blood is as concentrated as that recorded for monkeys. In works upon veterinary science numerous references both to physiological and pathological bleeding in the case of animals are to be found. Fleming, for example, observes that in the case of the cow "the hæmorrhagic flow appears two or three days after the commencement of rutting. The amount of blood does not exceed one or two ounces, and the coagulated clot remains in the vagina until it is expelled with the urine."

In the case of the primates the recognition of a regular and periodical menstrual discharge is of great antiquity. In fact, it is recorded by Dr. Mead that the ancient Egyptians painted the cynocephalus to represent the moon "upon account of a certain sympathy whereby the female of this animal has evacuations of blood from the uterus at the new and full moon." The subject of menstruation in the higher apes has been fully investigated by Heape, and his researches prove clearly that the pro-œstrum of primates is identical in kind with that of other mammals and is analogous to menstruation in the human female. The differences observed in individual species are only one of degree, relating either to occasional or regular rupture of vessels in the uterine mucosa, and partial or complete denudation of the latter. A comparative study of pro-œstrum from the lowest to the highest mammals shows a progressive development until in the primates and the human female the function reaches its highest state of development. Periodical uterine hæmorrhage is, in fact, one of the sacrifices which women must offer at the altar of evolution and civilisation.

The Menstrual Clot.

A study of the changes through which the uterus passes at each pro-œstrum reveals the interesting fact that in the great majority of those animals where this stage is characterised by a flow of blood from the endometrium, a definite and well-marked clot is formed in the body of the uterus. In fact, Heape, in his classification of the internal phenomena of pro-œstrum, accords the formation of the menstrual clot a definite place as one of the essential stages. In the case of the monkey he observes that " with the blood which is poured out from the ruptured lacunæ is mixed always degenerated epithelial cells, together with stroma tissue and the superficial portion of the uterine glands, the whole forming a more or less dense clot which in some cases entirely fills the uterine cavity. During the period of recuperation this clot is expelled." This is the case also in lemurs, but in the bitch no blood clot is formed. The physiological phenomena and anatomical appearances of the endometrium during pro-œstrum in the latter animal have been investigated in detail by Retterer, who notes that extravasation of blood in the mucosa occurs, but there is no denudation of the epithelium. It is a point of some interest, therefore, that a clot occurs where there is destruction of epithelium, or, in other words, where a definite breach of surface exists.

Menstrual Discharge in the Human Female.

As is well known, the normal menstrual discharge when it escapes from the vulva is a dark-red fluid containing epithelial débris, degenerate uterine glands, and leucocytes. It is usually stated that the blood does not clot. By some this is supposed to be due to dilution with the uterine and cervical secretions. It has also been stated that the mucous secretion from the cervix is the cause of the non-coagulation of the menstrual blood. In 1912 Blair Bell published a detailed analysis of retained menstrual fluid obtained from 12 cases of hæmatocolpos. In this material he found that fibrinogen and fibrin were absent, and therefore attributed the non-coagulation of menstrual blood to the absence of these constituents. On the other hand, in August, 1913, in a paper read before the Seventeenth International Congress of Medicine, J. Riddle Goffe attempted to show that the absence of coagulation was due to the presence of antithrombin in the menstrual blood. It is evident, therefore, that, although the fact of non-coagulation has been accepted, opinions are divided as to its causation.

A fluid similar in general appearance to that contained in hæmatocolpos is the coffee-coloured content of ovarian blood cysts. I therefore had a similar analysis made upon this material, and found that both fibrinogen and fibrin were again absent. A hæmoglobin derivative and very degenerated red cells were present, showing that the material primarily contained blood. A striking difference between the two fluids was the entire absence of calcium salts in the contents of the blood cyst and the superabundance of the same in hæmatocolpos fluid, as shown by Blair Bell. In the contents of an ovarian blood cyst that I recently investigated a small solid mass was present in the brown grumous fluid. This was investigated for fibrin by Weigert's method of staining, and small traces of this substance were present. In the rest of the fluid fibrin was absent. I am therefore led to the proposition that in the living body an enzyme or substance of this nature exists which has the power of digesting fibrin and breaking down blood clot. I hope to show, moreover, that a similar body or "fibrinolysin" plays a very important rôle both in the physiology and pathology of uterine hæmorrhage.

Since the formation of a menstrual clot is such a usual and common phenomenon amongst other species of mammalia, it was a matter of surprise to me that such should not be the case with the human female. The first investigation that I made, therefore, was to institute an inquiry amongst women as to the frequency with which they themselves had noted, at some time or other, the occurrence of clots or solid material in the normal menstrual discharge. The menstrual histories of 120 apparently healthy women were investigated, and of these 62 acknowledged that either occasionally or regularly they noted "clots" in the fluid. As a general rule these clots were minute, and unless a definite inquiry was made the fact was not observed by the patient, who casually observed that "the fluid did not clot." From this series, therefore, approximately 50 per cent. of women normally note the presence of clots in the menstrual discharge. The existence of these thrombi in the fluid proves that all the machinery for the coagulation of blood is complete.

It may not be out of place, in view of the remarks to follow, to state briefly the current views concerning the clotting of blood. Mellanby and Morawitz showed that normal blood plasma contains a globulin, fibrinogen, together with calcium salts and a substance of unknown composition designated prothrombin or thrombogen. The latter is in a condition of adsorption in the fibrinogen molecule. When blood leaves the vessels and is brought into direct contact with tissue cells it encounters a body known as thrombokinase. This substance, which varies in amount in different tissues, promotes the union of thrombogen and calcium salts to produce thrombin. The latter then exercises a quantitative action upon the fibrinogen, converting it into fibrin, the proteid which forms the organic basis of all clot. Excess of thrombin is inactivated by a hypothetical body called antithrombin normally circulating in healthy blood. It is obvious therefore that deficient or delayed coagulation may be produced by the individual absence of fibrinogen, prothrombin, calcium salts, thrombokinase, or excess of antithrombin.

An attempt to demonstrate the presence of excessive antithrombin in the non-menstruating and menstruating endometrium, and also in the menstrual fluid, failed in every case in a series of experiments which I undertook in conjunction with Dr. Gwynne Maitland, lecturer on physiology, University of Birmingham. The results of these experiments are detailed in Table I. and quite convinced us that excess of antithrombin is not the cause of non-coagulability of menstrual fluid.

The occurrence of a well-marked clot in each of these experiments points to the absence of any

TABLE I.—*Showing Results of Experiments undertaken to Ascertain Presence of Antithrombin in Menstrual Blood and the Endometrium.*

Series 1.

Experiment.	Curettings.	Human blood.	Coagulation.	Coagulation time.
	(Menstruating.)			
1	¼ vol.	1 c.c.	+	3 min.
2	¼ ,,	1 ,,	+	3½ ,,
3	½ ,,	1 ,,	+	2½ ,,
4	½ ,,	1 ,,	+	3 ,,
	(Non-menstruating.)			
5	¼ vol.	1 ,,	+	4 ,,
6	¼ ,,	1 ,,	+	3½ ,,
7	½ ,,	1 ,,	+	5 ,,
8	½ ,,	1 ,,	+	4 ,,
9	— Control.	2 ,,	+	5½ ,,
10	— ,,	2 ,,	+	5½ ,,

Series 2.

Experiment.	Filtrate from saline extract of endometrium.	Oxalate ox blood $+ CaCl_2$.	Coagulation.	Coagulation time.
	(Human, menstruating.)			
1	2 vols.	1 c.c.	+	6 min.
2	Equal vol.	1 ,,	+	6 ,,
3	½ vol.	1 ,,	+	5½ ,,
	(Human, non-menstruating).			
4	2 vols.	1 ,,	+	6 ,,
5	Equal vol.	1 ,,	+	5½ ,,
6	½ vol.	1 ,,	+	5 ,,
7	— Control.	1 ,,	+	6 ,,
8	— ,,	1 ,,	+	6½ ,,

Series 3.

Experiment.	Extract of endometrium.	Human blood.	Coagulation.	Coagulation time.
	(Sheep.)			
1	1 c.c.	1 c.c.	+	6 min.
2	1 ,,	1 ,,	+	5½ ,,
3	2 ,,	1 ,,	+	3 ,,
4	2 ,,	1 ,,	+	4 ,,
5	— Control.	2 ,,	+	5 ,,
6	— ,,	2 ,,	+	5½ ,,

Series 4.

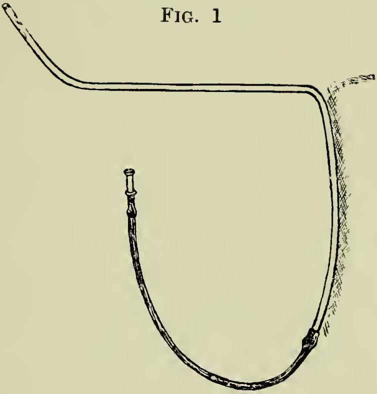
Experiment.	Menstrual blood. (Vaginal.)	Human blood.	Coagulation.	Coagulation time.
1	1 c.c.	1 c.c.	+	2½ min.
2	1 ,,	1 ,,	+	2 ,,
3	2 ,,	1 ,,	+	3 ,,
4	2 ,,	1 ,,	+	3½ ,,
	(Uterine.)			
5	1 ,,	1 ,,	+	2½ ,,
6	1 ,,	1 ,,	+	2½ ,,
7	2 ,,	1 ,,	+	3 ,,
8	2 ,,	1 ,,	+	2 ,,
9	— Control.	2 ,,	+	4½ ,,
10	— ,,	2 ,,	+	4 ,,

Material employed.—(*a*) Endometrium obtained by curettage during intermenstrual period; (*b*) ditto obtained during first and second days of period; (*c*) extracts of endometrium prepared from (*a*) and (*b*); (*d*) ditto prepared from animals (sheep); (*e*) menstrual blood collected from vagina and uterus.

antithrombin either in the endometrium or its secretion. Menstrual blood in sufficient quantities for experimental purposes is readily obtained from the vagina by placing the blade of a Sims's duck-bill speculum into the posterior cul-de-sac of the vagina, the patient lying in the Sims's semi-prone position. From material thus collected I have been able to convince myself that, although small clots are not infrequently present in the discharge, in the majority of cases the material is quite fluid and in essential details coincides with the analysis given by Blair Bell in the case of hæmatocolpos fluid. The points to which particular attention is drawn are : (*a*) the absence of fibrin ; (*b*) the usual absence of fibrinogen ; (*c*) the high proportion of calcium salts; and (*d*) the large number of leucocytes and occasionally lymphocytes scattered amongst the degenerated cells of the uterine epithelium and glandular débris. Normal menstrual blood in the vagina is faintly alkaline, and gives the spectrum of oxyhæmoglobin. Hæmolysis is practically always present.

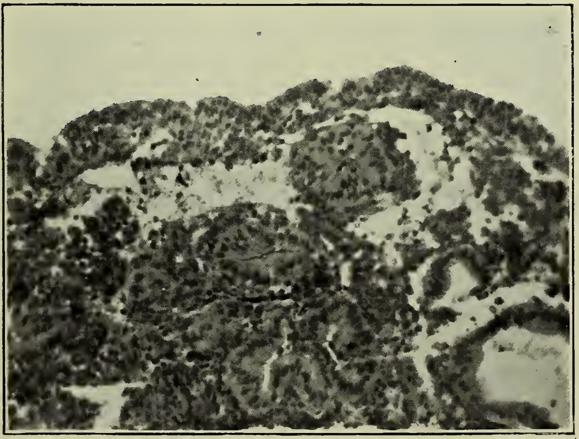
Material collected in the vagina, however, has very different characters from that taken directly from the uterus. In the first place, I venture to assert that *with the healthy and normal endometrium clotting always takes place within the uterine cavity.* This fact became evident to me when attempting to obtain menstrual fluid unmixed with the secretion from the cervical glands. The technique employed was as follows. The patient was placed in the semi-prone position and the posterior vaginal wall retracted with the broad blade of a Sims's speculum. The anterior lip of the cervix was seized with volsellum forceps and the cervix sterilised by iodine. A glass catheter of the shape and size indicated in Fig. 1 was introduced through the cervical canal into the corpus uteri. Where hæmorrhage is in progress this is a procedure of the greatest ease, and if the periodic flow is well established blood flows slowly into the tube. Within a few seconds, however, the stream ceases and an examination of the tube shows that the lumen is blocked by blood clot. Altogether 30 cases of normal menstruation have been examined by this means, usually upon the second day of the period when the flow is greatest, and in every case thrombus has

Fig. 1



Intra-uterine glass catheter for obtaining menstrual uterine secretion and blood directly from the uterine cavity. The catheter was made for the author by Messrs. Philip Harris and Co., Birmingham.

Fig. 2



Tissue of endometrium contained in normal menstrual blood (second day), and showing surface epithelium, glands, and stroma cells. The photograph proves that disintegration of tissue normally occurs and that a breach of surface exists.

been present in greater or less amount in the uterine cavity. In only 8 of these cases could fibrin be demonstrated in the blood present in the vagina. These details are represented in tabular form in Table II.

TABLE II.—*Showing Incidence of Thrombi in Uterine and Vaginal Blood.*

Case.	Age.	Day of period.	Clot in utero.	Clot in vagina.
1	28	2nd	+	−
2	21	2nd	+	−
3	34	2nd	+	−
4	26	1st	+	−
5	25	2nd	+	+
6	42	2nd	+	−
7	39	2nd	+	−
8	29	1st	+	−
9	16	2nd	+	+
10	24	3rd	+	+
11	22	2nd	+	−
12	44	2nd	+	−
13	39	2nd	+	+
14	15	1st	+	−
15	18	2nd	+	+
16	40	2nd	+	+
17	41	2nd	+	+
18	25	1st	+	−
19	36	2nd	+	−
20	35	3rd	+	−
21	40	1st	+	−
22	26	2nd	+	−
23	24	2nd	+	−
24	29	2nd	+	−
25	37	2nd	+	−
26	33	2nd	+	−
27	28	3rd	+	+
28	19	2nd	+	−
29	28	1st	+	−
30	46	2nd	+	−

At first I attributed this unexpected finding to direct trauma of the endometrium, but the continued presence of thrombi in spite of increased care in obtaining the blood, and the employment of tubes previously immersed in liquid paraffin, has convinced me that the phenomenon is physiological and a part of the menstrual cycle. In many cases the thrombus contains epithelial débris formed by breaking-down tissue from the endometrium, and so is analogous to the menstrual clot to which I have already referred in the case of primates. The microscopical appearances of a fragment of degenerated endometrium obtained from the menstrual clot are represented in Fig. 2. Since thrombi are not present in the fluid when it reaches the vagina, or if present are so small as almost to pass unnoticed, it is evident that during its passage from the corpus uteri to the lower genital passages fibrin becomes partially or completely dissolved. This autolysis is analogous to the phenomena I have referred to in the case of ovarian blood cysts, and in my opinion is the result of an enzyme of a fibrinolytic nature.

Evidence of a Specific Thrombolysin in the Uterine Secretion.

The question now arises as to whether it is possible to demonstrate the existence of such an enzyme by more conclusive tests. The experiments shown in Table III. were carried out with this in view. Menstrual blood collected from (*a*) the uterus and (*b*) the vagina was mixed in varied proportions with blood taken from the basilic vein. The coagulation time was noted and the tubes incubated at body temperature. The results are detailed as under :—

TABLE III.—*To show Thrombolytic Power of Menstrual Blood.*

Series 1. Menstrual Blood (Vaginal).

Experiment.	Venous blood.	Menstrual blood.	Coagulation time.	Clot resolved.	Time.
1	1 c.c. (auto).	1 c.c.	2 min	Partial.	12 hours.
2	1 ,, (hetero).	1 ,,	2½ ,,	Complete.	12 ,,
3	1 ,, (auto).	2 ,,	3 ,,	,,	12 ,,
4	1 ,, (hetero).	2 ,,	4 ,,	,,	10 ,,
5	1 ,, (auto).	3 ,,	2½ ,,	,,	12 ,,
6	1 ,, (hetero).	3 ,,	3 ,,	,,	12 ,,
7	1 ,, (auto).	½ ,,	4 ,,	Partial.	24 ,,
8	1 ,, (hetero).	½ ,,	5 ,,	Complete.	24 ,,
9	1 ,, (auto).	½ ,,	5 ,,	Partial.	24 ,,
10	1 ,, (hetero).	½ ,,	4 ,,	,,	24 ,,
11	1 ,, (auto).	¼ ,,	4½ ,,	,,	24 ,,
12	1 ,, (hetero).	¼ ,,	3 ,,	,,	24 ,,
13	2 ,, Control.	—	5 ,,	*Nil.*	24 ,,
14	2 ,, ,,	—	5½ ,,	,,	24 ,,
	Series 2. Menstrual Blood (Uterine).				
1	1 c.c. (auto).	1 c.c.	2½ min.	Complete.	48 hours.
2	1 ,, (hetero).	1 ,,	2 ,,	,,	24 ,,
3	1 ,, (auto).	2 ,,	3 ,,	Partial.	24 ,,
4	1 ,, (hetero).	2 ,,	2½ ,,	Complete.	12 ,,
5	1 ,, (auto).	3 ,,	3 ,,	,,	12 ,,
6	1 ,, (hetero).	3 ,,	2 ,,	,,	6 ,,
7	1 ,, (auto).	½ ,,	2½ ,,	Partial.	24 ,,
8	1 ,, (hetero).	½ ,,	2½ ,,	Complete.	24 ,,
9	1 ,, (auto).	½ ,,	3 ,,	,,	24 ,,
10	1 ,, (hetero).	½ ,,	4 ,,	Partial.	24 ,,
11	1 ,, (auto).	¼ ,,	4½ ,,	,,	24 ,,
12	1 ,, (hetero).	¼ ,,	5 ,,	,,	24 ,,
13	2 ,, Control.	—	4½ ,,	*Nil.*	24 ,,
14	2 ,, ,,	—	5 ,,	,,	24 ,,

In Table III. "auto" signifies that the venous blood and menstrual blood were collected from the same patient; "hetero" that the venous blood was taken from another patient. The coagulation time was estimated by Wright's coagulimeter method and also directly in test tubes, In the experiments quoted the coagulation times indicate that thrombosis was complete and that the test tube containing the mixed bloods could be inverted without the contents escaping.

With regard to the results, it will be noted that in the case of menstrual blood of vaginal origin the coagulation time of the mixture varied from 2 to 5 minutes. The resulting clot was resolved completely in 6 experiments and partially in the remaining 6 in times varying from 12 to 24 hours. With menstrual blood collected directly from the uterus coagulation occurred in from 2 to 4 minutes, the average time being 2·8 minutes. The resolution of clot took place completely in 7 cases and partially in the remaining 5. It should be noted, however, that in the latter, clot was already present before a further quantity of blood was added. With the controls no breaking down of clot occurred, and the coagulation time varied from 4½ to 5½ minutes. In those cases where resolution of the clot is recorded as complete the fluid was centrifugalised and the deposit stained for fibrin by Weigert's method. An important fact indicated in the table is that autolysis occurred not only with the patient's own blood, but also with that from another patient. The phenomenon is best marked where menstrual blood is in excess. When venous blood is in excess fibrinolysis is only partial.

A further series of experiments were undertaken to ascertain whether the substance present in menstrual blood, which possesses this power of disintegrating thrombi, acts in a quantitative manner or as a true enzyme. The results are detailed under Table IV., the object of these experiments also being to ascertain whether the fibrinolysin is in the fluid or solid portion of the menstrual discharge.

TABLE IV.—*To show Thrombolytic Power in the Fluid obtained by Centrifugalising Menstrual Blood.*

Series 1. Menstrual Blood (Vaginal). Fluid only.

Experiment	Venous blood.	Menstrual fluid.	Coagulation time.	Clot resolved.	Time.
1	1 c.c.	3 c.c.	3 min.	Complete.	12 hours.
2	1 ,,	2 ,,	2 ,,	,,	24 ,,
3	1 ,,	1 ,,	3 ,,	Partial.	24 ,,
4	1 ,,	½ ,,	4 ,,	,,	24 ,,
5	1 ,,	¼ ,,	3 ,,	*Nil.*	24 ,,
6	1 ,,	¼ ,,	5 ,,	,,	24 ,,
7	2 ,, Control.	—	5 ,,	,,	24 ,,
8	2 ,, ,,	—	5½ ,,	,,	24 ,,

Series 2. Menstrual Blood (Uterine). Fluid only.

1	1 c.c.	3 c.c.	3 min.	Complete.	24 hours.
2	1 ,,	2 ,,	3 ,,	,,	12 ,,
3	1 ,,	1 ,,	2 ,,	,,	6 ,,
4	1 ,,	½ ,,	4 ,,	Partial.	24 ,,
5	1 ,,	¼ ,,	4 ,,	*Nil.*	24 ,,
6	1 ,,	¼ ,,	3½ ,,	Partial.	24 ,,
7	2 ,, Control.	—	5 ,,	*Nil.*	24 ,,
8	2 ,, ,,	—	5 ,,	,,	24 ,,

The material for these experiments was obtained by centrifugalising menstrual blood from the uterus and vagina. The fluid in the case of the uterus was clear or only faintly stained with hæmoglobin; that from the vagina, on the other hand, was always dark red in colour due to an extreme degree of hæmolysis. In the case of those experiments where complete resolution of clot occurred the fluid was again centrifugalised and the supernatant liquid mixed with fresh normal blood and incubated at body temperature. The results of this further series are shown in Table V.

TABLE V.—*To show Thrombolytic Power in Menstrual Fluid after Thrombolysis has occurred. Fluid again Centrifugalised.*

Experiment.	Venous blood.	Menstrual blood.	Coagulation time.	Clot resolved.	Time.
1	1 c.c.	2 c.c.	4 min.	Partial.	24 hours.
2	1 ,,	1 ,,	3 ,,	,,	,,
3	1 ,,	1 ,,	4 ,,	*Nil.*	,,
4	1 ,,	½ ,,	4½ ,,	,,	,,
5	1 ,,	¼ ,,	5 ,,	,,	,,
6	1 ,,	—	4 ,,	,,	,,
7	2 ,, Control.	—	5 ,,	,,	,,

It appears, therefore, that the body producing thrombolysis is present in the fluid portion of the menstrual discharge, and, moreover, acts in a quantitative manner, since it will not produce the resolution of an unlimited amount of thrombus. Its power becomes gradually less in material obtained by repeated autolysis and centrifugalisation. Furthermore, the fibrinolysin present in the menstrual discharge appears to be specific, since it does not exert any very evident action upon fibrin obtained in the usual manner from ox blood as shown in the following series of observations (Table VI.).

TABLE VI.—*To show Fibrinolytic Power of Menstrual Blood upon Ox Fibrin.*

Experiment.	Menstrual blood.	Source.	Fibrin dissolved.	Time.
1	4 c.c.	Vagina.	? Partial.	24 hours.
2	3 ,,	,,	,,	,,
3	2 ,,	,,	*Nil.*	,,
4	1 ,,	Uterus.	,,	,,
5	½ ,,	,,	,,	,,
6	½ ,,	,,	,,	,,

In these experiments a single thread of fibrin was employed, and in only two was there any evidence of solution. In these the fluid after incubation became very tenacious and tarry, resembling the contents of hæmatocolpos both in consistency and colour. The fibrin thread, however, only partially disappeared, and therefore the experiments cannot be considered conclusive. Digestion of ox blood fibrin with varying quantities of other fluids, for example, extract of endometrium, extract of ovary, hydrocele fluid, and fluid from parovarian and pseudo-mucinous cysts, also all proved negative. The question naturally arises as to whether the thrombolytic property of menstrual fluid is due to any of the known constituents of the latter. Blair Bell has shown that calcium salts are present in the menstrual discharge in excess of those present in the circulating blood. The fluid also contains mucin secreted by the cervical glands and small quantities of lactic and butyric acids. The results obtained in a series of experiments undertaken to ascertain the effect of these substances upon the coagulation time of blood and the possession of any thrombolytic power are shown in Table VII.

TABLE VII.—*To show the Effect of Mucin, Calcium Salts, Lactic and Butyric Acids upon the Coagulation of Blood.*

Series A. Mucin.

Experiment.	Mucin 2 % sol.	Venous blood.	Coagulation time.	Clot resolved.	Time.
1	½ c.c.	1 c.c.	25 min.	*Nil.*	24 hours.
2	1 ,,	1 ,,	30 ,,	,,	24 ,,
3	2 ,,	1 ,,	35 ,,	,,	24 ,,
4	3 ,,	1 ,,	35 ,,	,,	24 ,,
5	4 ,,	1 ,,	40 ,,	,,	24 ,,
6	— Control.	2 ,,	5½ ,,	,,	24 ,,

N.B.—Clot formation delayed and thrombus soft in consistency.

Series B. Calcium Chloride.

Experiment.	Calcium chloride 1 c.c.	Venous blood.	Coagulation time.	Clot resolved.	Time.
1	0·5 %	1 c.c.	7 min.	*Nil.*	24 hours.
2	1 ,,	1 ,,	15 ,,	,,	24 ,,
3	2 ,,	1 ,,	30 ,,	,,	24 ,,
4	3 ,,	1 ,,	*Nil.*	,,	24 ,,
5	4 ,,	1 ,,	,,	,,	24 ,,
6	5 ,,	1 ,,	,,	,,	24 ,,
7	Saturated.	1 ,,	,,	,,	24 ,,
8	— Control.	2 ,,	5 min.	,,	24 ,,

Series B. Calcium Chloride.

Figures given by Wright (quoted by Addis).

0·018% $CaCl_2$	…………	Blood failed to clot. ? Cause.
0·036 ,, ,,	…………	Clots in 1½ min.
0·055 ,, ,,	…………	,, 1 ,,
0-110 ,, ,,	…………	,, 2½ ,,
0·165 ,, ,,	…………	,, 5 ,,
0·183 ,, ,,	…………	,, 6½ ,,
0·366 ,, ,,	…………	,, over 60 min.
0·550 ,, ,,	…………	,, Fails to clot in 24 hours.

N.B.—Menstrual blood yielded an ash equivalent to 1·44% total solids and calcium 8 parts CaO per 6000 (0·133%).

Series C. Lactic Acid.

Experiment.	Lactic acid 1%.	Venous blood.	Coagulation time.	Clot resolved.
1	¼ c.c.	1 c.c.	10 min.	*Nil.*
2	½ ,,	1 ,,	25 ,,	,,
3	1 ,,	1 ,,	30 ,,	,,
4	2 ,,	1 ,,	*Nil.*	,,
5	3 ,,	1 ,,	,,	,,
6	4 ,,	1 ,,	,,	,,
7	— Control.	2 ,,	5½ min.	,,

Series D. Butyric Acid.

Experiment.	Butyric acid 1%.	Venous blood.	Coagulation time.	Clot resolved.
1	¼ c.c.	1 c.c.	7½ min.	*Nil.*
2	½ ,,	1 ,,	8 ,,	,,
3	1 ,,	1 ,,	30 ,, (slight).	,,
4	2 ,,	1 ,,	*Nil.*	,,
5	3 ,,	1 ,,	,,	,,
6	4 ,,	1 ,,	,,	,,
7	– Control.	2 ,,	5½ min.	,,

Since observing the phenomenon of thrombolysis in menstrual blood I have investigated several pathological fluids from the same standpoint. I do not wish to go into detail on the present occasion, but in passing I may say that from material obtained from various ovarian cystomata the fluid which appears to possess the best marked thrombolytic power is that contained in lutein cysts. This is interesting in view of the supposed lutein origin of ovarian blood cysts. and the observation that I have already noted as to the absence of fibrin and fibrinogen from the contents of such cysts. It is probable that thrombolysins play an important part in the living organism in removing products of diffuse hæmorrhage and thrombosis. A body of this nature certainly appears to occupy a definite rôle in the physiology of menstruation by rapidly and easily removing the results of intra-uterine coagulation.

Summarising, therefore, the preceding facts, it appears necessary for descriptive purposes to classify the menstrual discharge under two headings—viz., (1) contents of the uterus; and (2) contents of the vagina. The former consist of thrombus containing epithelial cells, leucocytes, and calcium salts, mixed with the secretion from the uterine glands containing fibrinolysin. The fluid is alkaline in reaction and gives the spectrum of oxyhæmoglobin. The contents of the vagina consist of the products of thrombolytic and hæmolytic digestion, mixed with vaginal cells and the secretions of the corporeal and cervical glands. A considerable amount of mucus is present with traces of lactic and butyric acids. The fluid possesses a faint but distinct odour, and is alkaline in reaction. In colour it is dark red and gives the spectrum of oxyhæmoglobin. Micro-organisms abound in the fluid contained in the vagina, but are rare in material obtained from the uterine cavity.

The Influence of Thrombokinase in Promoting the Clotting of Menstrual Blood.

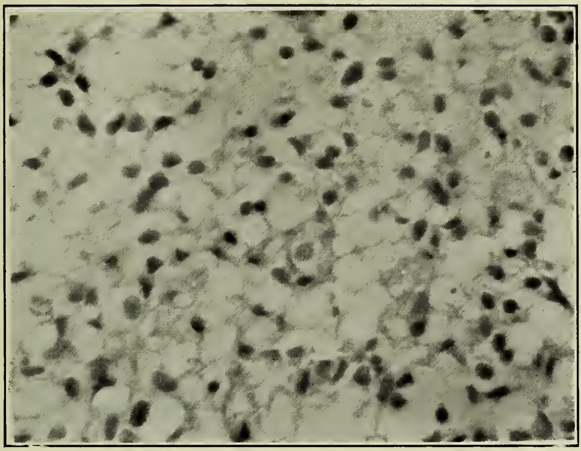
Rapid clotting of the blood in the tissues of the endometrium is undoubtedly facilitated by the thrombokinitic power of the endometrial stroma. In the results of experiments detailed in Tables I. and III. it was shown that both the tissue of the endometrium and menstrual blood have the power of diminishing the coagulation time of normal blood. This phenomenon I attribute to an excess of thrombokinase derived from the stroma cells. In the results contained in Table VII. I have shown that rapid clotting is not aided by any of the known constituents of the menstrual fluid in such proportions as occur in the latter. On the other hand, it is well known that extracts of certain tissues, such as the testis, have the power of lowering the coagulation time of blood. In the case of the uterine endometrium this specialisation of function and storage of thrombokinase subserves a very important physiological purpose. It must be remembered that under normal conditions hæmorrhage from the menstruating endometrium is a slow ooze, and there is ample time for the blood to be brought into relation both with the stroma cells which contain the thrombotic elements, and the secretion of the uterine glands which brings about thrombolysis. The high thrombokinitic power of the endometrium is therefore a provision of nature to facilitate clotting and prevent excessive hæmorrhage. Even in well-marked cases of hæmophilia profuse uterine hæmorrhage very rarely occurs during menstruation, as recorded by Gulland and Goodall. This to my mind is a very strong clinical argument in favour of the views that I have just put forward.

Thrombokinitic power of the endometrium is present both in the non-menstruating and menstruating uterus, but appears to be most marked in the latter. Clinically the phenomenon is often evident during the operation of curetting. It is well known how rapidly the blood clots when mixed with the curetted endometrium, and special precautions are necessary to obtain tissue for microscopical purposes unmixed with clot. If, now, the curettings are incubated at body temperature partial or complete thrombolysis occurs according to the proportion of tissue and thrombus present. When curettage is performed during a menstrual period thrombolysis appears to be much more active.

The Histological Characters of the Menstruating Endometrium.

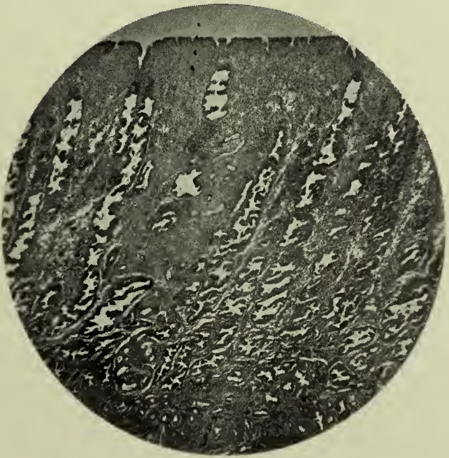
Considerable attention has been given within recent years to the anatomical study of the endometrium in the human female, both during the state of rest and during the phases of actual menstruation. Young, in 1911, pointed out that the stroma of the endometrium is to be regarded as a sponge-like structure formed by the union of branching processes from the individual cells, and he suggested that the extravasation of blood into the intercellular spaces is due to metabolic changes taking place within the cells, initiated in all probability by the stimulus of a hormone of ovarian origin. Since the appearance of Young's work I have examined numerous sections of endometrium obtained by operation, and have satisfied myself that his views as regards the development of a

Fig. 3



Stroma of endometrium under high magnification to show branching processes of stroma cells and formation of a reticulum.

Fig. 4



Normal diffuse hypertrophy of endometrium (superficial portion). Superficial glands irregular and dilated; deep glands do not take part in the premenstrual hypertrophy.

reticulum from the cells of the endometrial stroma are correct. Details in structure are best seen during the early pre-menstrual stage before hæmorrhage occurs into the stroma. The individual cells at this period are widely separated from each other, as shown by Fig. 3, and the identity of the so-called reticulum with the branching processes of the individual stroma cells is quite evident.

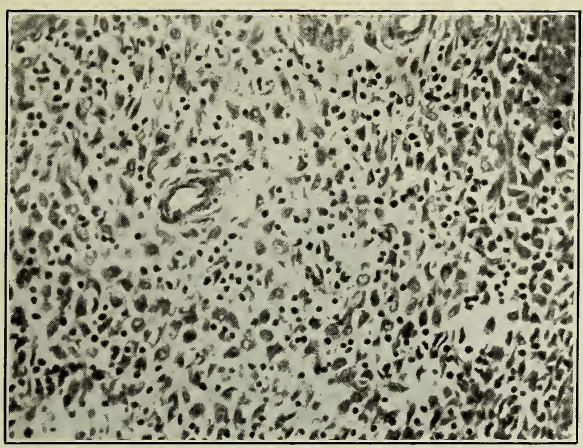
More recently, Adler and Hitschmann have described in detail the histological characters of the endometrium during the complete menstrual cycle. They point out that the cycle is divided into three stages—viz., pre-menstrual, menstrual, and post-menstrual—the essential changes affecting both the glandular and stroma elements in the endometrium. During the menstrual flow there is a definite loss of epithelium both from the glands and surface of the endometrium. After menstruation an extraordinary formation of new cells occurs, correlating to the amount of tissue lost. This continues until the end of the interval before the succeeding menstruation, when the newly formed epithelium is anatomically complete. Physiological function is then developed, as shown by the production of secretion in the glands. At this stage they are large and dilated, with intraglandular processes composed of high columnar secreting epithelium. At the termination of the function, on the other hand, the glands are small, narrow, and long, and the epithelium low.

The appearance exhibited by glands during the pre-menstrual stage is shown in Fig. 4. It is important to note that apparently only the superficial portion of the endometrium takes part in the active changes during the acme of the cycle. The stroma in relation to the metrium, although congested, does not exhibit under normal conditions the same œdema and hæmorrhage as the superficial layer. It appears, therefore, to act as a rearguard, whose duty it is to replace the tissue lost during the destructive stage. The superficial stroma cells of the endometrium hypertrophy during the premenstrual period, and present a more or less similar appearance to the decidua of an early pregnancy. (Fig. 5.)

Occasionally this "decidual reaction" is extremely marked, as shown in Fig. 6, which represents a portion of the curettings obtained from a single girl, aged 23, the operation being performed for dysmenorrhœa. In this particular instance no question of pregnancy could be entertained. Blair Bell has drawn attention to a similar appearance sometimes noted in the "casts" of the uterus passed by patients the subject of so-called membranous dysmenorrhœa or exfoliative endometritis. The view that I hold is that this disease merely represents an extremely high grade of development of what in a lesser degree is a normal anatomical occurrence, and in a sense may be regarded as an atavistic phenomenon. These "casts" are almost precisely identical with the menstrual clot and complete denudation of the endometrium which is present in the higher apes.

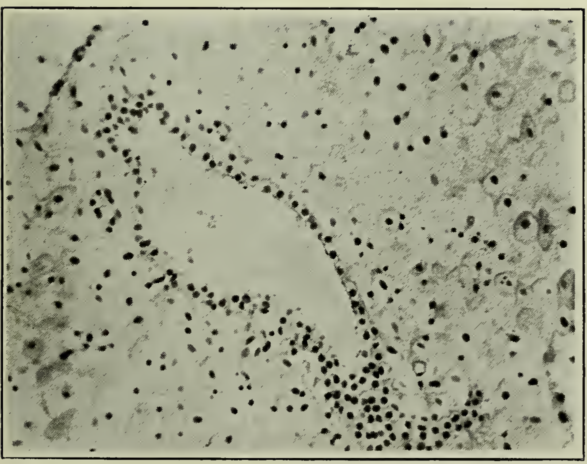
Adler and Hitschmann remark that when the development of the endometrium is completed, if pregnancy does not take place, hæmorrhage occurs simply because the glands in the mucosa throw out their secretion. In other words, the loss of blood indicates the termination of the physiological cycle. This hæmorrhage is associated with shedding of portions of the superficial endometrium, both stroma and glands. That destruction of the tissue definitely occurs is shown by Fig. 2, which represents tissue found in the clot collected from the

FIG. 5



Early premenstrual decidual change in superficial cells of stroma of endometrium. Note branching of cells and large nuclei.

FIG. 6



Well-marked "decidual" change in stroma cells during normal menstruation. Section taken from surface of endometrium.

uterine cavity before cytolysis has taken place. Gland epithelium and stroma cells are quite evident.

The facts, therefore, to which special emphasis should be directed are the following: 1. Physiological enlargement and dilatation of the uterine glands during the pre-menstrual stage. 2. The formation of a modified decidua by the superficial cells of the stroma. This, as a rule, is only partial. 3. Hæmorrhage following the complete development of the endometrium associated with partial disintegration of the superficial layers of both glandular epithelium and stroma. 4. A period of regeneration dating from the stage of post-menstrual destruction to the development of a new layer of secreting epithelium and fresh decidua. Correlating these facts with the statements already made upon the biochemical function of the endometrium, I would observe that under physiological conditions hæmorrhage does not occur until both stroma and glands are at their highest grade of development; in other words, both factors are present and physiologically balanced to control uterine bleeding and dispose of the clot so produced.

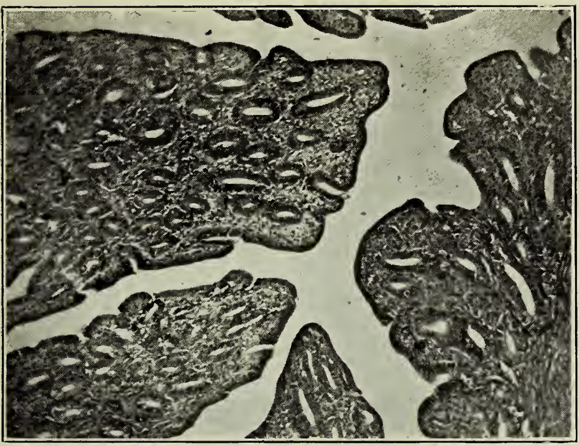
Factors in the Production and Cessation of the Menstrual Hæmorrhage.

Before an inquiry can be instituted into the question of pathological bleeding it is a matter of the highest importance to ascertain if possible the machinery concerned in the control of normal menstrual hæmorrhage. Three factors suggest themselves as having a possible influence upon such a question—viz., (1) The effect of uterine muscular contractions in limiting the supply of blood flowing to the endometrium; (2) the action of a hormone or hormones producing capillary dilatation in utero; and (3) the biochemical function of the endometrium itself.

As regards the first named, it has been stated that such contractions are present, and that if the uterus is palpated during the progress of the menstrual flow it is not infrequent to note periodic variations in its consistency. Direct demonstration of this fact is of course difficult in the human subject, but in the case of rabbits Blair Bell has recorded that extreme uterine contractions are produced by the injection of uterine secretion. I have also observed the occurrence of direct peristaltic movements in the uteri of rabbits when the secretion obtained from an artificial hydrometra is administered intravenously. Is it possible, therefore, that a portion of the uterine secretion is reabsorbed and serves as a direct stimulus to uterine contraction, thus diminishing the amount of blood flowing to the endometrium?

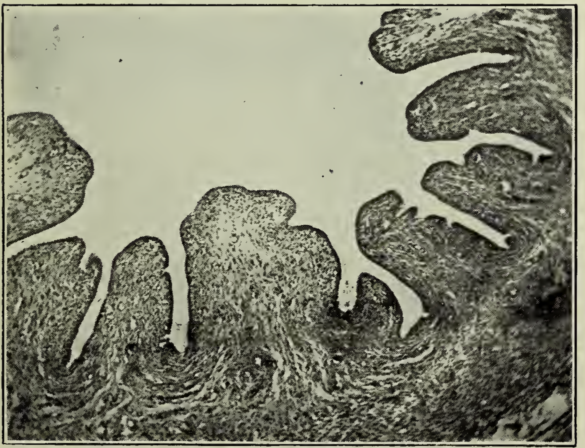
Bond has gone very carefully into the chemical composition of the uterine secretion in rabbits obtained from an artificial hydrometra. He found that the fluid was clear and watery in appearance with a low specific gravity, and that it held a large quantity of sodium chloride in solution. During pregnancy this secretion was absent. Also, in those animals where the uterine cornua were ligated Bond noted that the period of œstrum was prolonged and occurred frequently. I am at present carrying out an investigation in rabbits into the physiological properties of the uterine secretion obtained by Bond's method, with a view to ascertaining the effect, if any, of this secretion upon the production of œstrum and the control of hæmorrhage. The

FIG. 7



Hydrometra in rabbit. Activity of uterine glands. Note dilatation of glands.

FIG. 8



Hydrometra in rabbit after double oöphorectomy. Shows atrophy of endometrium.

results so far obtained are sufficiently interesting to place before you.

Experiment I.—Virgin rabbit, weight 1570 grm. On Dec. 9th, 1913, both uterine cornua were ligated and a third ligature passed around the upper end of the vagina. The wound healed in a few days, and on Dec. 19th the animal was placed with the buck. Coitus occurred almost daily until Jan. 12th, when the animal was killed Both uteri were distended and 3 c.c. of fluid were collected under aseptic precautions. The pelvic viscera and vagina were much congested and the animal was evidently experiencing œstrum. The activity of the uterine glands is shown well in Fig. 7, representing a section through the uterus of this animal compared with Fig. 8, showing a section through the uterus of an animal during the period of anœstrum.

Of the uterine secretion 1 c.c. was immediately mixed with 1 c.c. of the animal's blood. Clotting was complete in 1½ minutes. The control clotted completely in 3½ minutes.

Experiment II.—Mature virgin rabbit, weight 1580 grm. Not "on heat." The animal was inoculated on Jan. 14th, 1914, into the tissues of the thigh with 2 c.c. of the turbid opalescent uterine secretion obtained from Experiment I. The animal was examined the following day and signs of pro-œstrum were present. The following day the abdomen was opened and the pelvic viscera inspected. The uterus was swollen and congested and evidently in œstrum. One cornu of the organ was excised for microscopical examination, and the other was ligated as in Experiment I. in order to obtain a fresh supply of material.

Experiment III.—Virgin rabbit, weight 1305 grm. On Dec. 12th, 1913, ligation of the right uterine cornu was carried out, the left cornu being left in communication with the vagina. Ten days later the animal was placed with the buck, and it was again noted that coitus occurred at once and almost daily till the date on which it was killed, Jan. 13th, 1914. A well-marked hydrometra of the right uterine cornu was present, and 3 c c. of turbid opalescent fluid were collected with aseptic precautions. 1 c.c. of the fluid was placed with 1 c c. of blood. Clotting was complete in

2 minutes. The control clotted in 4½ minutes. The left cornu was much congested and in a state of œstrum. No pregnancy was present.

Experiment IV.—Virgin rabbit, weight 1295 grm. On Jan. 14th. 1914, the animal was inoculated into the tissues of the thigh with 1 c.c. of uterine secretion obtained from Experiment III. On the following day an examination did not show any evident sign that the animal was "on heat." On the second day after operation the abdomen was opened and the pelvic organs examined. Congestion of the uterus and vagina was present, but not to the extreme degree found in Experiment II. It appeared that œstrum was commencing and not fully established. One cornu was excised for microscopical examination; the other was ligated in order to obtain a further supply of secretion.

Experiment V.—Virgin rabbit, weight 1950 grm. On Dec. 16th, 1913, double oöphorectomy was performed, with ligation of both uterine cornua at their junction with the vagina. Ten days later the animal appeared in good health and was placed with the buck. Coitus occurred regularly, and in fact no difference was noted between this animal and the two others in which the ovaries had not been removed. The animal was killed on Jan. 12th, 1914. A small hydrometra was discovered in both uterine cornua, but only 1½ c.c. of fluid could be obtained from the same. The pelvic organs were not markedly congested and the uterine secretion had a different appearance to that noted in the two normal animals. It was a clear watery fluid, not turbid, and when added to an equal quantity of rabbit's blood produced no alteration in the coagulation time.

Experiment VI.—Mature virgin rabbit, weight 1320 grm. Not "on heat." On Jan. 14th, 1914, the animal was inoculated into the muscles of the thigh with 1 c.c. of uterine secretion obtained from Experiment V. No point of interest was noted upon the following day, and two days after the inoculation the pelvic organs were inspected through an abdominal incision. They appeared normal and not congested. One uterine cornu was excised for microscopical examination and the endometrium showed no evidence of marked activity, the glands being small and contracted. Double oöphorectomy was performed and the remaining uterine cornu ligated in order to obtain a further supply of material if possible.

The experiments, as far as the investigation has gone, appear to show that the uterine secretion in rabbits, at least, is under the control of the ovaries both as to amount and physiological action. The normal secretion apparently aids coagulation of the blood—a point of interest when it is remembered that pro-œstrum in this animal is not associated as a rule with external hæmorrhage. The secretion also appears to stimulate œstrum. Bond's experiments have shown that when the fluid is pent up, as in artificial hydrometra, œstrum is frequent and prolonged, and my investigations certainly tend to confirm his observations. It appears possible, therefore, that uterine secretion, stimulated and controlled by an ovarian hormone, is partly absorbed and produces that dilatation of vessels which is characteristic of the late stages of pro-œstrum and immediately precedes œstrum. Whether this is the case with the human female it is only possible to surmise, but with the close analogy of menstruation to pro-œstrum it is certainly possible. At the same time, clinical experience has shown that a period of œstrum or sexual desire may occur in the human species quite independently of both uterus and ovaries, as is the case when these organs have been removed singly or together at an early period of married life. The subject is naturally difficult to investigate from a scientific standpoint, and observations are most reliable when based upon animal experiments.

Concerning heterogeneous extracts prepared from the uterine endometrium and from the ovarian stroma and corpus luteum, I have been unable to satisfy myself that these have any effect in stimulating the onset of œstrum or in accelerating menstruation. At my request Messrs. Burroughs and Wellcome kindly prepared for me extracts of uterine endometrium and ovary from tissues obtained from the sheep. A series of rabbits were inoculated daily with these extracts in doses of 1 c.c. for a period of 28 days. At the end of this time the animals were killed and the pelvic organs, suprarenal and thyroid glands, subjected to detailed macroscopical and microscopical examination. The results as regards the uterus and ovaries are shown in Table VIII.

The uterus and ovaries in these six animals, with the exception of Rabbit 2, presented no difference, either to the naked eye or under the microscope, to the same organs of two control animals. All were in an anœstrus condition, showing no congestion and no recently ruptured Graafian follicles. Rabbit 2 cannot be included in the results owing to the fact that it was pregnant when the experiment commenced. I conclude, therefore, that extracts of the endometrium and ovary of the sheep have no physiological effect in stimulating œstrum in the case of the rabbit.

Similar negative results were observed in the case of six women who received intramuscular injections of these extracts during the premenstrual period. No alteration was noted either in the duration of the cycle or length of the actual menstrual period. Whether these results would be modified by extracts prepared from organs during a period of sexual activity it is impossible at present to say. Such extracts are difficult to obtain in quantities sufficient for experimental purposes.

Be this as it may, there is ample evidence available to show that normal pro-œstrum and menstruation are under the control of the ovary and its associated endocrinous glands. It is superfluous on my part to dwell upon this aspect of the subject, which has been so admirably investigated within recent years. In particular, I would refer to the work of Biedl, Blair Bell, and Harvey Cushing. In the light of such knowledge we cannot say that menstruation is dependent solely upon ovarian function, although the latter is undoubtedly the strongest link in the chain. We must recognise the fact that the function of this organ is influenced by other elements in that great endocrinous system. A further reference to this subject will be made when discussing pathological uterine hæmorrhage.

TABLE VIII.—*To show Effect of Extracts of Sheep's Endometrium and Ovary containing Corpus Luteum upon the Uterus and Ovaries of Rabbits.*

Rabbit.	Initial weight.	Weight at death.	Extract.	Uterus.	Ovaries.
1	1730 grm.	2012 grm.	Endometrium.	Normal.	Normal.
*2	1830 ,,	1790 ,,	,,	Large and congested.	Recent corpus luteum.
3	770 ,,	945 ,,	Ovary.	Normal.	Normal.
4	970 ,,	1135 ,,	,,	,,	,,
5	1390 ,,	1500 ,,	Endometrium and ovary.	,,	,,
6	1430 ,,	1425 ,,	,,	,,	,,

* This animal aborted after the eleventh injection. It was not known to be pregnant when the experiment was commenced.

PATHOLOGICAL UTERINE HÆMORRHAGE.

In considering excessive uterine bleeding apart from gross physical signs, the first point I would emphasise is that the amount of red uterine discharge cannot be regarded as a criterion of the severity of hæmorrhage and as an index of the quantity of blood lost. The admixture with uterine secretion and the occurrence of hæmolysis introduce difficulties, and it is therefore impossible to fix a standard of the actual amount of blood lost. We can estimate the total quantity of menstrual fluid, but to differentiate between the amounts of the two chief constituents—viz., secretion of the uterine glands and blood—no means are at present available. The colour of the discharge is but a rough index and is obscured by alteration of hæmoglobin through admixture with the vaginal secretions. A differential blood count is useless because we have no standard with which to compare our results; centrifugalisation and measurement of the deposit is unreliable owing to the varying degree of hæmolysis and cytolysis. Hæmoglobin in menstrual fluid is dark, and owing to hæmolysis a very small quantity serves to colour a large amount of secretion. It follows therefore that an alleged severe hæmorrhage may consist largely of the secretion of the uterine glands with a comparatively small admixture of blood.

Two factors remain upon which we can form an approximate opinion of the degree of hæmorrhage. The first and most important is the clinical effect produced upon the patient by the supposed bleeding. If, in spite of repeated severe losses, she remains in good health and shows no degree of anæmia, we may assume that the uterine discharge consists chiefly of the secretion of the glands rather than excess of blood. The second factor is the occurrence of clots in the discharge. These are, of course, direct evidence of the amount of blood lost, and in severe hæmorrhages are usually present. Their occurrence indicates either (1) that the uterine secretion is deficient in thrombolysin; or (2) that too large a quantity of blood is present for the thrombus to be digested by the available enzyme; or (3) that the escape of blood from the surface of the endometrium is too rapid for the fluid to come in contact with the fibrinolysin present in the uterine secretion. I believe that all of these factors are at different times concerned in the occurrence of clotting in the menstrual discharge. Nature's ideal is to produce an exact balance between the thrombotic and thrombolytic functions of the endometrium, but that this equilibrium is easily upset is shown by the fact that 50 per cent. of all women at some time or other in their lives pass clots.

Factors in the Production of Excessive Bleeding.

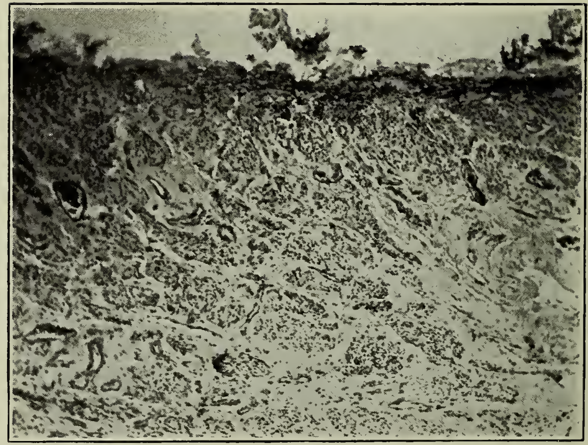
A consideration of the essential machinery involved in the production of uterine hæmorrhage suggests that excessive bleeding may arise from: (1) factors in relation with the endometrium; (2) factors associated with the endocrinous glands, especially the ovary. To these two primary groups I would add a third—viz., factors concerned in the abnormal production of pelvic venous stasis. It appears probable that under Group 1 are included many cases of so-called menorrhagia, whilst Groups 2 and 3 are more closely related to metrorrhagia or intermenstrual bleeding. At the same time these groups undoubtedly overlap with the production of irregular hæmorrhage, so that it is not possible to draw any hard-and-fast line.

The Endometrium in Relation to Pathological Uterine Hæmorrhage.

When discussing the physiology of menstruation I attempted to prove that under normal conditions the degree of uterine hæmorrhage is very much under the control of the endometrium. As the blood escapes into the tissues it is brought into contact with cells rich in thrombokinase, and this induces rapid coagulation. The thrombus is then disintegrated by the enzyme contained in the secretion of the corporeal glands. These two processes are normally balanced, but it will be obvious that abnormalities in either may lead to the production of excessive bleeding. I would suggest that cases of pathological hæmorrhage of endometrial origin fall under one of the two following headings: (*a*) Diminished thrombokinitic power of the endometrium from a deficiency of thrombokinase; (*b*) hypersecretion of the uterine glands, producing excess of thrombolysin.

It is possible to bring forward clinical evidence that both these factors are concerned in the production of extreme uterine hæmorrhage. I do not wish to occupy your time in detailing clinical notes, but I may observe that on several occasions when collecting blood from the vagina in cases of severe menorrhagia I have noted that a few clots have appeared in the fluid on standing. This phenomenon appeared strange until I appreciated the fact that it was simply a delay in the normal function of clotting

Fig. 9



Atrophied endometrium in case of diffuse fibrosis uteri. Hæmorrhage was profuse and necessitated hysterectomy.

due to diminution in amount in one of the essential constituents for the production of thrombin. In these cases clots form in the vagina instead of in the uterine cavity. They escape with the menstrual fluid, and if large are noted by the patient. Frequently quite large clots are passed without any pain, the reason being that the thrombi are formed in the vagina and do not pass through the cervical canal. If curettage is performed in these cases it is not infrequently found that the endometrium is atrophic and very little tissue can be removed. This is so with the fibrotic uterus and with the atrophy of old age. (Fig. 9.) Hæmorrhage when it occurs under these conditions is severe because the essential factors for controlling the same are absent.

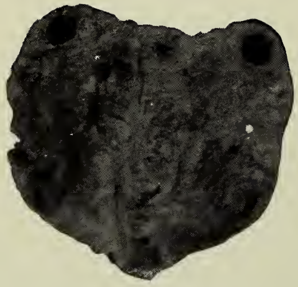
The second factor that I have noted in the production of extreme bleeding is hypersecretion of the uterine glands. I can conceive that variations occur both in regard to the amount of this discharge and in the concentration of thrombolysin in a normal quantity of secretion. An allusion has already been made to the fact that such excessive secretion may lead to error in estimating the amount of blood lost from the uterus. It is probable that this excess also at times leads to a destructive action upon the protective thrombus in relation with the endometrium. Thrombosed capillaries are rendered patent and the hæmorrhage continues just so long as the secretion is poured out in excessive quantities. The clinical type of case that I will lay before you as an example of this mode of bleeding is the condition variously described as "diffuse adenoma," "adenomatosis," or simply "glandular hypertrophy of the endometrium." When the menstrual fluid of such patients is investigated I have found that clots are rarely present. The discharge is always profuse and thrombolytic power well marked. In passing, it is of interest to note that excessive thrombolysis probably accounts for the profuse hæmorrhage occurring with a simple adenomatous polypus. In such polypi the glandular elements are usually in considerable excess in the stroma. When protective thrombosis occurs the clot is dissolved by the secretion of the abnormal glands and a recurrence of the hæmorrhage ensues. After all, a mucous polypus is simply a localised variety of the major condition of diffuse glandular hypertrophy.

The Importance of Investigation of the Menstrual Discharge.

It appears desirable, therefore, that a careful investigation should be made of the discharge in every case of obscure uterine bleeding. I am afraid that there has been a tendency to avoid such examination in the past, partly no doubt owing to a wish to respect the feelings of the patient. In the presence of severe hæmorrhage, however, I have never encountered the least objection on the part of patients when the necessity for such examination was placed before them. The points in the investigation to which special attention should be directed are: (1) The presence or absence of thrombi within the vagina; (2) the formation of thrombi within the discharge after the fluid has been allowed to stand; (3) the thrombolytic power of the secretion; (4) the calcium content of the same; and (5) the microscopical characters of the deposit obtained after centrifugalisation of the fluid collected directly from the uterine cavity in order to obtain an index of the degree of tissue destruction.

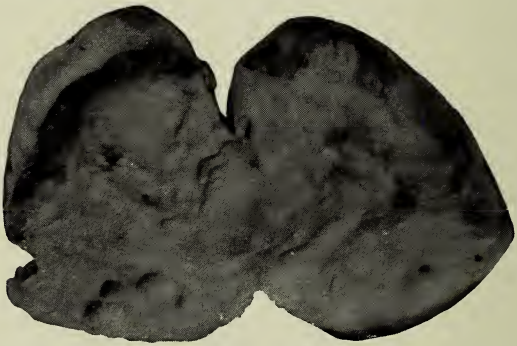
Fig. 10

A



Normal ovary from nullipara, aged 32.

B



Hyperplasia of ovary from nullipara, aged 32. Hyperplasia principally affects stroma : Graafian follicles few and small.

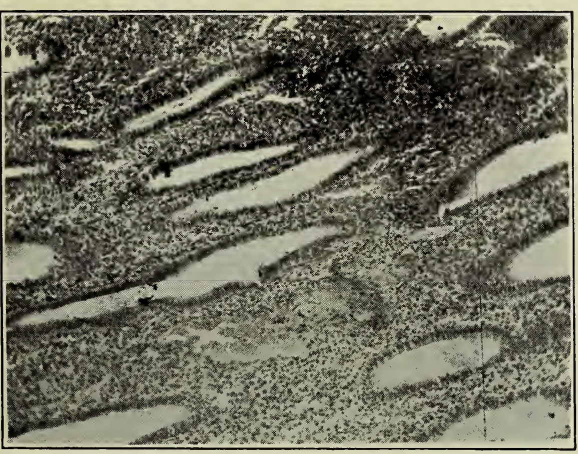
Influence of the Endocrinous Glands upon Uterine Hæmorrhage.

Time will not permit me to enter at length into a full consideration of the intricate relationship which the endocrinous glands bear to the question of uterine hæmorrhage, nor is it my desire to do so, since I can add very little that is new to the mass of facts that have accumulated within recent years upon the interaction of the various hormones.

Since uterine hæmorrhage in the human female is in such intimate relationship with the activity of the uterine glands, it follows that factors which produce alteration in the function of these glands will also cause anomalies in the former. The organs chiefly concerned in this are, of course, the ovaries, and their removal usually leads to cessation of menstruation. Proof is gradually accumulating which tends to show that in a considerable number of cases the cause of excessive uterine hæmorrhage lies in the ovary. Quite recently three cases have come under my notice where double ovarian hyperplasia was associated with extreme overgrowth of the endometrium and profuse irregular uterine hæmorrhage. Curettage had been performed in two of these cases, with relief lasting for about nine months. At the end of this time the bleeding recurred in all its original severity. Fig. 10 shows a photograph of one of the ovaries removed from a lady, aged 32, who had suffered from very extreme bleeding since puberty. Marriage had aggravated the condition, and when I saw her she was suffering from an extreme degree of secondary anæmia. By the side of the hyperplasic organ I have placed a normal ovary from a patient of the same age, the difference in size being very apparent. Such hyperplasia, I believe, may be a developmental abnormality at puberty. At times also it appears to be associated with masturbation and sexual excess, but its real cause is difficult to define. The endometrium in these cases is very hypertrophic and shows marked activity of the glandular elements, as indicated in Fig. 11.

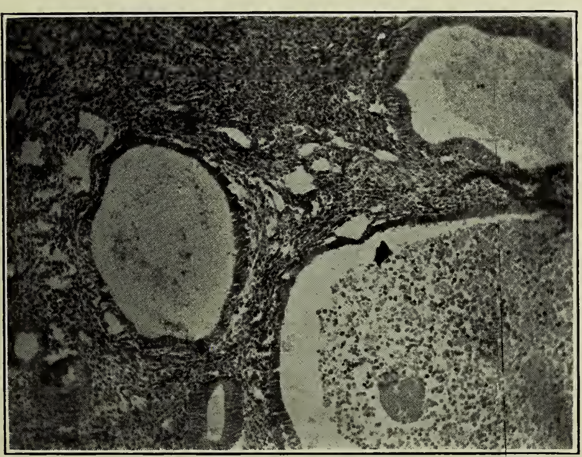
I have already referred to the influence the ovary appears to have over the amount and physiological properties of the secretion of such glands. If, in the future, it is proved that a portion of the uterine secretion is reabsorbed and produces vaso-dilatation, one of the factors in the production of uterine hæmorrhage can be removed by reducing the quantity of ovarian secretion. Also, by diminishing the thrombolytic element, another of the essential factors productive of prolonged hæmorrhage is placed in abeyance. Physiological and pathological evidence therefore appears to point to the fact that partial removal of the ovaries is indicated in very excessive and uncontrollable uterine hæmorrhage associated with glandular hypertrophy. At the same time it should be recognised that even double oöphorectomy does not control every case of uterine bleeding. Whether this is due to a transference of ovarian function to another of the endocrinous glands, particularly the thyroid, or whether it is due to defects in the uterus itself, it is impossible at present to state with certainty. We know, for example, that the thyroid frequently hypertrophies after the normal or artificial menopause. There is also evidence to show that sexual desire is not lost after removal of both ovaries alone or with the uterus. On the other hand, the continuation of bleeding in the presence of definite uterine

Fig. 11



Endometrium showing dilatation of glands and hæmorrhage into stroma. Condition resembles premenstrual stage of normal endometrium.

Fig. 12



Endometrium, active. Glands large and cystic; leucocytes and epithelial débris in lumina; stroma infiltrated with red blood cells.

lesions, more particularly fibrosis, when both ovaries have been ablated, points to the uterine condition as being the essential cause of the hæmorrhage in such cases.

Whatever the stimulus to menstruation may be, whether ovarian or a combination of ovarian and other hormones, it appears from the examination of numerous curettings obtained *in abnormal cases of uterine hæmorrhage, that all portions of the endometrium are not affected in the same manner at the same time.* This is well shown in Figs. 12 and 13 which represent different aspects of curettings from the same uterus. It will be noticed that in Fig. 12 the glands are large and the endometrium in an active stage. In Fig. 13, on the other hand, the adenomatous elements are small, the stroma abundant, and the tissue evidently in the post-menstrual stage. This, I believe, has a distinct bearing upon the duration of uterine hæmorrhage, In curettings taken from a comparatively normal uterus during a period of short duration all portions of the endometrium appear alike and correspond to the active stage described by Adler and Hitschmann, When hæmorrhage lasts for 10 to 14 days, however, the endometrium frequently shows very different appearances at different parts of the section. There has been a tendency to regard this appearance as a definite lesion in the endometrium and call it by that well-worn and long-suffering term "endometritis." This I regard as erroneous. There is no evidence of inflammation when such sections are stained for plasma cells, and the appearance is, I believe, produced by the ovarian hormone acting in small quantities over a lengthy period and stimulating the endometrium to activity in sections. Clinically, such cases not infrequently follow labour and abortion, and account for many of the examples of menorrhagia and irregular bleeding which occur at intervals remote from pregnancy, but apparently dating from the same. Curettage in such cases reveals no products of conception, and the reason for the bleeding is often obscure. I suggest that the cause lies in a functional defect of the delicate mechanism called into action at each menstrual period.

The same is apparent at the commencement and end of sexual life. The balance is extremely sensitive, and when once disturbed by any of the great physiological epochs of life—viz., puberty, pregnancy, or the menopause—a considerable degree of tuning up is required before it is in complete working order.

Hæmorrhage at Puberty and at the Menopause.

As is well known, the two extremes of sexual life are very frequently marked by excessive uterine hæmorrhage. When consideration is given to the various factors that I have discussed in the production and control of bleeding, this is really not a matter of great surprise. The reason that excessive hæmorrhage occurs in young girls is probably because the hormonic stimulus is developed before the means of controlling its results are elaborated; in other words, it is a lack of development in which both endometrium and possibly metrium take part. In those cases of hæmorrhage at puberty where I have examined the uterine discharge, clots have been present in the vagina in a large proportion. In two no clot was present in the uterus, although small clots were found in the fluid contained in the vagina. This suggests delayed coagulation of the fluid due to deficient thrombokinitic power of the endometrium, the result of functional non-development. The great majority of these cases get well and radical measures are very rarely called for. Curettage is occasionally performed, but as a rule without permanent success. This is explained on the pathological basis I have suggested above.

A similar condition prevails at the other extremity of sexual life. The balance is again upset, but on this occasion the loss of function is due to atrophy and degeneration rather than to lack of development. It appears that in many cases the ovarian function is the first to light its fire and the last to be extinguished. Should its hormone be active after the endometrium with its thrombokinase has atrophied and the musculature in the metrium is degenerated, hæmorrhage invariably results. The very extreme and profuse losses that occur at this period of life are practically always associated with numerous clots. Hæmorrhage occurs rapidly although a loose clot may be present in the uterine cavity. The condition, in fact, in many ways bears a close resemblance to the oozing from a wound in a subject of hæmophilia.

HÆMORRHAGE IN RELATION WITH ORGANIC DISEASE OF THE INTERNAL SEXUAL ORGANS.

The last portion of my lecture deals briefly with the subject of uterine hæmorrhage in connexion with organic disease of the internal sexual organs. This aspect of the subject is, of course, a very large one, and in the short time at my disposal it is impossible to do anything like adequate justice to the facts. I have arranged the material in tabular form (Table IX.) as being most convenient for reviewing rapidly the relationship which uterine hæmorrhage bears to the diseases involved. The material employed for this table was obtained from

Table IX. (*a*).—*Showing Incidence of Excessive Uterine Hæmorrhage in Relation with Organic Disease of the Internal Sexual Organs* :—

A.—Uterus.

M. = married. S. = single.

		Cases.	Menorrhagia.	Metrorrhagia.
(*a*) Displacements.				
Retro-displacements.				
Simple	M.	34	15	4
	S.	16—50	4—19 (38%)	4—8
Complicated with—				
(*a*) Adhesions		27	10	4
(*b*) Endometritis		4	4	3
(*c*) Prolapse of ovary		2	1	0
(*d*) Rupture of perineum		2	1	0
(*e*) Hæmorrhoids		1	1	0
(*f*) Torsion of spleen		1	1	0
(*g*) Mucous polypus		1—38	1—19 (50%)	0—7
Anteflexion.				
Simple	M.	0	0	0
	S.	3—3	0—0	0—0
Complicated with—				
(*a*) Vaginismus		1	1	0
(*b*) Metritis		1—2	1—2	1—1
Procidentia.				
Degree—1st	M.	22	3	0
	S.	1—23	0—3	0—0
,, 2nd	M.	32	5	1
	S.	3—35	1—6	0—1
,, 3rd	M.	29	4	1
	S.	2—31	0—4	0—1
Grand total (procidentia)		89	13 (14·6%)	2
(*b*) Fibrosis and chronic metritis—				
Metritis		18	15	11
Fibrosis—				
(*a*) Hypertrophic		8	8	4
(*b*) Atrophic		1—27	—23 (85·1%)	1—16
(*c*) Endometritis	M.	61	46	24
	S.	12—73	10—56 (76·7%)	5—29

(*d*) Hypertrophy of endometrium—	Cases.	Menorrhagia.	Metrorrhagia.
Localised (mucous polypus)	18	17	13
Diffuse (glandular hypertrophy)	10—28	10—27 (96·4 %)	10—23
B.—Ovaries.			
(*a*) Cystomata*—			
Cyst-adenoma (multilocular cyst)	56	11	5
Pseudo-myxoma	2	0	0
Papillomatous	13	3	1
Follicular	4	2	3
Lutein	6	3	2
Dermoid	11	0	0
Parovarian	8—100	1—20 (20 %)	0—11
(*b*) Malignant neoplasm—			
Carcinoma	12	2	1
Sarcoma	1—13	0—2 (15·3 %)	0—1
(*c*) Prolapse of ovaries	6	2	2
(*d*) Hyperplasia of ovaries	3	3	3
C.—Pelvic Inflammation.			
(*a*) Fallopian tubes—			
Salpingitis	9	3	0
Hydrosalpinx	5	1	0
Pyosalpinx—			
Single	8	4	1
Double	27	13	5
Hæmatosalpinx	3—52	1—22 (42·3 %)	1—7
(*b*) Ovaries—			
Salpingo-oöphoritis	36	18	8
Tubo-ovarian cyst or abscess	2	0	0
Hæmatoma of ovary	10	6	2
Ovarian abscess	4	1	0
Suppurating lutein cyst	11	5	2
Suppurating cyst-adenoma	1—64	0—30 (46·8 %)	0—12
(*c*) Peritoneum—			
Pelvic peritonitis—			
(1) Simple	20	5	1
(2) Tuberculous	9	1	0
(3) Pneumococcal	1	0	0
Pelvic abscess	30—60	9—15 (25 %)	3—4

* Of the 20 cases (cystomata of ovaries) associated with excessive hæmorrhage 1 was due to fibroid polypus, 5 had always noted menorrhagia, 3 were connected with the menopause, and 2 dated the irregular bleeding from a recent pregnancy. One was associated with plumbism, and another with inflammatory disease in the pelvis. The percentage of hæmorrhage due to cause unknown is therefore only 7.

TABLE IX. (*b*).—*Summary of Table IX.* (*a*).

Uterus.	Cases.	Excessive hæmorrhage.	Percentage.
(*a*) Displacements—			
Retro-displacements—Simple	50	19	38
Complicated	38	19	50
Anteflexion—Simple	3	0	0
Complicated	2	2	0
Prolapse	89	13	14·6
Total displacements	182	53	29·1
(*b*) Fibrosis	27	23	85·1
(*c*) Endometritis	73	56	76·7
(*d*) Hypertrophy of endometrium—			
Localised (polypus)	18	17	94·4
Diffuse	10	10	100·0
Total	310	159	51·2
Ovaries.			
(*a*) Cystomata	100	20	20
(*b*) Malignant neoplasm	13	2	15·3
(*c*) Prolapse	6	2	33·3
(*d*) Hyperplasia	3—122	3—27	100—22·1
Pelvic Inflammation.			
(*a*) Fallopian tubes	52	22	42·3
(*b*) Ovaries	64	30	46·8
(*c*) Pelvic peritonitis	60—176	15—67	25—38

TABLE IX. (*c*).—*Contrasting the Incidence of Menorrhagia in Uterine, Ovarian, and Inflammatory Disease.*

	Cases.	Excessive hæmorrhage.
Diseases of uterus	310	51·2%
Diseases of ovaries (including inflammation)	186	30%
Inflammatory diseases (Fallopian tubes and peritoneum)	112	33%

the case-books of all patients admitted to the gynæcological wards of the General Hospital, Birmingham, during the years 1909–1913. I am much indebted to Professor Thomas Wilson for the use of the same.

The following classification has been employed :—I. Uterus : (*a*) displacements ; (*b*) fibrosis and chronic metritis ; (*c*) endometritis. II. Ovary : (*a*) cystomata ; (*b*) malignant neoplasms ; (*c*) displacements ; (*d*) hypertrophy. III. Pelvic Inflammation : (*a*) Fallopian tubes ; (*b*) ovary ; (*c*) peritoneum. The information derived from the table may be summarised as follows.

Uterus.

1. *Uterine displacements.*—It is evident that displacements of the uterus do not directly produce excessive uterine hæmorrhage. Thus, out of a total of 88 cases of retro-displacements only 38 gave evidence of menorrhagia, and of the latter only 15 had intermenstrual losses. In those cases where hæmorrhage was present a careful review of the case histories did not show that the displacement was more acute than in patients where no bleeding was present. On the other hand, the proportion of irregular bleeding is considerably greater in the complicated cases than in those that are simple. With prolapsus uteri it was found that out of a total of 89 cases only 13 showed evidence of excessive bleeding. It appears therefore that uterine displacements cannot be regarded as a cause of excessive losses.

2. *Fibrosis and chronic metritis.*—This condition of obscure origin is in a very large proportion of cases associated with uterine bleeding. Thus, in a total of 27 cases, 23 suffered from menorrhagia. It is interesting to note that in my series all the patients were married. In a paper recently com-

municated to the Obstetrical Section of the Royal Society of Medicine, I have drawn attention to the fact that some cases of fibrosis uteri appear to bear a relationship to syphilis; thus out of a total of 16 cases, 7, or 43·75 per cent., gave a positive Wassermann reaction. Attention has also been drawn to this aspect of the subject by Miss McIlroy.

Sir John Bland-Sutton has suggested that fibrosis uteri is the result of septic infection and is analogous to the fibrosis of the Fallopian tubes seen in chronic pyosalpinx. This view is certainly feasible, since the majority of cases occur in those patients who have run the risk of infection by repeated pregnancy or otherwise. At the same time it is strange that the infecting agent should remain in the uterus and not spread upwards to the Fallopian tubes and peritoneum. In my experience it is rare for the Fallopian tubes to show signs of any inflammation. Also in a series of 12 cases of fibrosis uteri that were examined bacteriologically by Dr. Sholto Douglas (of the University of Manchester) and myself, cultures from the uterine cavity invariably proved sterile. Such an argument, however, is not conclusive evidence that the fibrosis is *not* the result of old infection, since the causal agent may be dead or so attenuated as to be unrecognisable by the bacteriological methods at our disposal.

Hæmorrhage in cases of fibrosis uteri is probably due to two factors: (*a*) changes in the endometrium to which reference has already been made; and (*b*) loss of contractility of the metrium owing to its replacement by fibrous tissue. The amount of blood conducted to the endometrium cannot be regulated, and the latter is powerless to deal with the quantity at its disposal.

3. *Endometritis.*—In the figures concerned with endometritis it will be noted that out of a total of 73 cases 56 were associated with menorrhagia and 29 with metrorrhagia. These figures, I firmly believe, are fallacious and due to a misapprehension of what we now know to be the characteristics of true inflammation of the endometrium to which the term "endometritis" should alone be applied. The subject has recently been very fully discussed by Adler and Hitschmann, and with the views set forward by these writers I cordially agree.

A thorough investigation of the cases classed clinically as "endometritis" showed that 61 of the patients were married, and of these 43 directly attributed the irregular hæmorrhages to the last labour or abortion at intervals varying from 3 months to 1 year. The irregularity, in fact, dated from the resumption of function. Examination of the curettings revealed the following facts: (*a*) 25 cases showed what in the past was designated "glandular endometritis"; (*b*) 9 cases showed all the characteristics of the so-called "interstitial endometritis" of Ruge's classification; (*c*) atrophic "endometritis" was present in 2; (*d*) plasma cells and marked leucocytic infiltration appeared in 7. In other words, 34 exhibited only evidence of those changes which we now know to be but physiological, and therefore could not be classed as "endometritis."

Endometritis of septic origin does not appear to produce uterine hæmorrhage. Thus, in a series of 15 cases where curettage was performed for discharge and pain, the endometrium was infiltrated with plasma cells and leucocytes. Hæmorrhage was absent. In one of these cases, where the discharge was very foul and the clinical diagnosis was "putrid endometritis," thrombosis of the vessels was present as shown in Fig. 14. Furthermore, every case where hæmorrhage accompanied a true "endometritis," as shown by the presence of plasma cells, the curettings invariably exhibited a combination of different phases of the menstrual cycle; in other words, the hæmorrhage in these cases was, in my opinion, not due to the endometritis, but rather to a functional defect in the ovarian hormone. Such is the case in Figs. 12 and 13, which represent different portions of the endometrium from the same uterus obtained at one curetting.

4. *Hypertrophy of the endometrium.*—It is unnecessary to dwell further upon the relation of hypertrophy of the endometrium to uterine hæmorrhage. In its diffuse form it occurs under the name of "glandular hypertrophy"; its localised variety is the common "adenomatous polypus." Hæmorrhage is usually profuse and appears to be due to excessive thrombolysis of the uterine clot.

Ovary.

5. *Ovarian cystomata.*—Reference to the preceding table shows that cystomata of the ovary rarely cause interference with the menstrual function. This is a matter for some surprise, since it might be expected that as the function is so much under the control of these organs wide variations would occur. It must, however, be remembered that the hormone is probably produced by the cells of the stroma, whilst cystomata are in many cases related to the Graafian follicles.

6. *Displacements of the ovary.*—Displacements of this organ as a general rule do not produce excessive uterine hæmorrhage. However, in some cases

of extreme congestion of the organs associated with simple retroversion I have at times been tempted to attribute the excessive losses to this cause, since correction of the retroversion by pessary treatment without relief to the prolapsed ovary produced no amelioration in the severity of the uterine bleeding.

7. *Hypertrophy of the ovary.*—Reference has previously been made to this condition in the course of the lecture, and its close association with hypertrophy of the endometrium and profuse hæmorrhage defined. It is important to note that the hypertrophy affects the stroma rather than the Graafian follicles, and the close association of the condition with hypertrophy of the endometrium appears to afford clinical evidence that it is from the ovarian stroma that the specific hormone is derived.

Pelvic Inflammation.

8. Pelvic inflammation is not infrequently associated with excessive hæmorrhage from the uterus. Thus in 176 cases we find that 67, or 38 per cent., are accompanied by menorrhagia. In the figures quoted there appears to be little difference between inflammatory processes attacking the Fallopian tubes and those involving the ovaries. It might be thought that lesions affecting the ovaries would produce greater anomalies in the menstrual function. At the same time we must remember that it is only in the most extreme cases of inflammatory disease that the whole of both ovaries is disintegrated, and we know both from experimental and operative results that a very minute portion of ovarian tissue is sufficient to maintain the regularity of the menstrual function.

Furthermore, the majority of inflammatory processes are insidious in their onset and afford ample time for ovarian function to be assumed by other elements in the endocrinous system if it be agreed that such transference of function takes place.

As regards the occurrence of excessive bleeding in pelvic inflammatory disease, I am more inclined to think that the hæmorrhage is the result of interference with the venous return rather than to any specific effect either upon endometrium or ovary, since it occurs not only in connexion with inflammatory lesions related to the sexual organs, but also in cases secondary to extra-genital inflammation, such as appendicitis. Furthermore, treatment applied either directly to the endometrium or ovary usually fails in such cases.

It is not my intention to discuss those factors which I have included under Group 3 in the incidence of pathological uterine hæmorrhage—viz., pelvic venous stasis. I have referred to this aspect of the subject on other occasions, and no useful purpose will be served by detailing facts already recorded.

PRINCIPLES OF TREATMENT.

I conclude with a brief reference to the therapeutics of pathological hæmorrhage based upon the physiological and pathological principles to which I have referred.

Curettage.

In the first place, I may say a few words concerning the operation of curettage. For many years the curette has held a high position in the treatment of excessive hæmorrhage from the uterus. When the immediate and remote results of this operation are considered, however, we find that although a certain proportion of patients are permanently cured, a considerable percentage exists where the benefit derived is only temporary; thus Buzze, quoted by Adler and Hitschmann, has published the after-histories of 500 cases curetted because of hæmorrhage attributed to "chronic endometritis." He found that only 10 per cent. were *permanently* cured. In considering the value of this operation we are led to the conclusion that cases fall under one of three groups: (*a*) Cases where cure is permanent; (*b*) cases where relief is temporary, hæmorrhage recurring after a greater or less interval; and (*c*) cases where no benefit accrues.

Group (*a*) includes cases where hæmorrhage is due to a localised cause, such as a mucous polypus. It also includes those patients who in the interval following temporary relief recover the physiological balance which I have already indicated as being essential for the control of periodical hæmorrhage.

Group (*b*): Hypertrophy of the endometrium falls under this heading, and the reason that relief is only temporary is partly because the primary defect is often not situated in the uterus. With the removal of the hypertrophic endometrium the bleeding ceases for a time. Within a few months, however, if the stimulant is still acting, hypertrophy again takes place and hæmorrhage recurs.

Group (*c*) includes those cases where curettage is performed for hæmorrhage due to errors in the functional power of the endometrium itself, more particularly hæmorrhages associated with puberty and the menopause. In such cases very little tissue is removed with the curette, and the hæmorrhage continues practically from the day of the operation.

What then *is* the value of curettage in the therapeutics of uterine hæmorrhage? I would say that its use is principally for diagnostic purposes. If the examination of the curetted endometrium is taken in conjunction with an analysis of the menstrual discharge, and care taken to correlate the appearances of the endometrium with the period of the sexual cycle, much valuable information may be gained as to the cause of a specific hæmorrhage. Curettage at the two extremes of sexual life is, in my opinion, a useless procedure except for diagnostic purposes. It is not possible to alter the character of the endometrium by any amount of curetting. This is proved by examination of repeated curettings from the same uterus, and it accounts for the fact that in glandular hyperplasia of the endometrium curettage is only of temporary benefit.

Indications for Treatment.

Treatment to be successful must be based upon a physiological and pathological basis. Thus, where hæmorrhage is due to the absence of thrombokinase, such as occurs in menorrhagia due to the atrophy of old age, attempts may be made to replace the same. In the case of puberty natural cure usually takes place within a few months by development of the endometrium, and in the great majority of patients there is no necessity for local treatment. At the menopause, however, if hæmorrhage is very profuse or prolonged, the application of thrombokinase in the form of extract of endometrium or extract of testicle is useful in immediately controlling the same. Fibrin ferment directly applied to the endometrium is also of service in directly checking hæmorrhages of this nature. (Fibrin ferment, similar to that employed in my experiments, is supplied by Messrs. Parke, Davis, and Co. under the name of "coagulose.")

If bleeding is due to excessive thrombolysis, the result of hyperplasia of the endometrium, temporary relief may be obtained by curetting. If bleeding recurs I would suggest that partial oöphorectomy be performed. This procedure has answered admirably in those cases that have come under my notice where profuse losses are associated with high thrombolytic power and extreme hypertrophy of the endometrium. Where hæmorrhage appears to be the result of venous stasis appropriate means must be taken to relieve the same, either by purgation in the case of portal congestion or operation where the cause is severe and chronic inflammation.

In those cases where the uterus has lost its power of regulating the supply of blood to the endometrium, such as in fibrosis or arteriosclerosis, hysterectomy appears to be the safest and best method of treatment.

In conclusion, I have one duty more. It is to tender my most sincere thanks to my friend and colleague at the General Hospital, Birmingham, Professor Thomas Wilson, for the very valuable help he has afforded me throughout the whole of my investigations both as regards facts, material, and friendly criticism. I am also under the deepest obligation to Professor R. F. C. Leith and Professor E. Wace Carlier, of the University of Birmingham, in whose laboratories the majority of the experimental work for this lecture has been carried out. I have also to thank Dr. Gwynne Maitland and Dr. Cranston Walker for very valuable assistance in the physiological aspects of the subject, Dr. med. Esther Kadisch for help with the literature, and numerous other friends without whose loyal coöperation the work could not have been accomplished.

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